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*Valproic acid* may increase the exposure to nifedipine during concomitant therapy. Blood pressure should be monitored and a dose reduction of nifedipine considered.

*Phenytoin, Phenobarbital, and Carbamazepine:* Nifedipine is metabolized by CYP3A. Coadministration of nifedipine 10 mg capsule and 60 mg nifedipine coat-core tablet with phenytoin, an inducer of CYP3A, lowered the AUC and C<sub>max</sub> of nifedipine by approximately 70%. Phenobarbital and carbamazepine are also inducers of CYP3A. Alternative antihypertensive therapy should be considered in patients taking phenytoin, phenobarbital, and carbamazepine.

#### Antiemetic Drugs

*Dolasetron:* In patients taking dolasetron by the oral or intravenous route and nifedipine, no effect was shown on the clearance of hydrodolasetron.

#### Immunosuppressive Drugs

*Tacrolimus:* Tacrolimus has been shown to be metabolized via the CYP3A system. Nifedipine has been shown to inhibit the metabolism of tacrolimus *in vitro*. Transplant patients on tacrolimus and nifedipine required from 26% to 38% smaller doses than patients not receiving nifedipine. Nifedipine can increase the exposure to tacrolimus. When nifedipine is coadministered with tacrolimus the blood concentrations of tacrolimus should be monitored and a reduction of the dose of tacrolimus considered.

*Sirolimus:* A single 60 mg dose of nifedipine and a single 10 mg dose of sirolimus oral solution were administered to 24 healthy volunteers. Clinically significant pharmacokinetic drug interactions were not observed.

#### Glucose Lowering Drugs

*Pioglitazone:* Coadministration of pioglitazone for 7 days with 30 mg nifedipine ER administered orally q.d. for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 to 0.95) for C<sub>max</sub> and 0.88 (0.80 to 0.96) for AUC relative to nifedipine monotherapy. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

*Rosiglitazone:* Coadministration of rosiglitazone (4 mg b.i.d.) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine.

*Metformin:* A single dose metformin-nifedipine interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C<sub>max</sub> and AUC by 20% and 9%, respectively, and increased the amount of metformin excreted in urine. T<sub>max</sub> and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin.

*Miglitol:* No effect of miglitol was observed on the pharmacokinetics and pharmacodynamics of nifedipine.

*Repaglinide:* Coadministration of 10 mg nifedipine with a single dose of 2 mg repaglinide (after 4 days nifedipine 10 mg t.i.d. and repaglinide 2 mg t.i.d.) resulted in unchanged AUC and C<sub>max</sub> values for both drugs.

*Acarbose:* Nifedipine tends to produce hyperglycemia and may lead to loss of glucose control. If nifedipine is coadministered with acarbose, blood glucose levels should be monitored carefully and a dose adjustment of nifedipine considered.

#### Drugs Interfering with Food Absorption

*Orlistat:* In 17 normal-weight subjects receiving orlistat 120 mg t.i.d. for 6 days, orlistat did not alter the bioavailability of 60 mg nifedipine (extended release tablets).

#### Dietary Supplements

*Grapefruit Juice:* In healthy volunteers, a single dose coadministration of 250 mL double strength grapefruit juice with 10 mg nifedipine increased AUC and C<sub>max</sub> by factors of 1.35 and 1.13, respectively. Ingestion of repeated doses of grapefruit juice (5 x 200 mL in 12 hours) after administration of 20 mg nifedipine ER increased AUC and C<sub>max</sub> of nifedipine by a factor of 2. Grapefruit juice should be avoided by patients on nifedipine. The intake of grapefruit juice should be stopped at least 3 days prior to initiating patients on nifedipine.

#### Herbals

*St. John's Wort:* St. John's Wort is an inducer of CYP3A and may decrease exposure to nifedipine. Alternative antihypertensive therapy should be considered in patients in whom St. John's Wort therapy is necessary.

#### CYP2D6 Probe Drug

*Debrisoquine:* In healthy volunteers, pretreatment with nifedipine 20 mg t.i.d. for 5 days did not change the metabolic ratio of hydroxydebrisoquine to debrisoquine measured in urine after a single dose of 10 mg debrisoquine. Thus, it is improbable that nifedipine inhibits *in vivo* the metabolism of other drugs that are substrates of CYP2D6.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility:

Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. **There is a literature report of reversible reduction in the ability of human sperm obtained from a limited number of infertile men taking recommended doses of nifedipine to bind to and fertilize an ovum in vitro.** *In vivo* mutagenicity studies were negative.

#### Pregnancy

Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placental, teratogenic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m<sup>2</sup> basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

From the clinical evidence available, a specific prenatal risk has not been identified. However, an increase in perinatal asphyxia, caesarean delivery, prematurity and intrauterine growth retardation have been reported.

Careful monitoring of blood pressure must be exercised in pregnant women, when administering nifedipine in combination with IV magnesium sulfate due to the possibility of an excessive fall in blood pressure which could harm the mother and fetus.

There are no adequate and well-controlled studies in pregnant women.

#### Nursing Mothers

Nifedipine is excreted in human milk. Nursing mothers are advised not to breastfeed their babies when taking the drug.

#### Pediatric Use

The safety and effectiveness of nifedipine extended-release tablets in pediatric patients have not been established.

#### Geriatric Use

Although small pharmacokinetic studies have identified an increased half-life and increased C<sub>max</sub> and AUC (See **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism**), clinical studies of nifedipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### Patients with Galactose Intolerance

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### ADVERSE EXPERIENCES

The incidence of adverse events during treatment with nifedipine extended-release tablets in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on nifedipine extended-release tablets and in 64 of the 126 patients on placebo. All adverse events reported during nifedipine extended-release tablets therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with nifedipine extended-release tablets was peripheral edema. This was dose related and the frequency was 18% on nifedipine extended-release tablets 30 mg daily, 22% on nifedipine extended-release tablets 60 mg daily and 29% on nifedipine extended-release tablets 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include:

NIFEDIPINE EXTENDED- RELEASE TABLETS (%) (n=370)	PLACEBO (%) (n=126)	
<b>Adverse Event</b>		
Headache	19	13
Flushing/heat sensation	4	0
Dizziness	4	2
Fatigue/asthenia	4	4
Nausea	2	1
Constipation	1	0

Where the frequency of adverse events with nifedipine extended-release tablets and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

**Body as a Whole/Systemic:** chest pain, leg pain

**Central Nervous System:** paresthesia, vertigo

**Dermatologic:** rash

**Gastrointestinal:** constipation

**Musculoskeletal:** leg cramps

**Respiratory:** epistaxis, rhinitis

**Urogenital:** impotence, urinary frequency

Other adverse events reported with an incidence of less than 1.0% were:

**Body as a Whole/Systemic:** allergic reaction, asthenia, cellulitis, substernal chest pain, chills, facial edema, lab test abnormal, malaise, neck pain, pelvic pain, pain, photosensitivity reaction

**Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, migraine, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectases

**Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, hypesthesia, insomnia, somnolence

**Dermatologic:** angioedema, petechial rash, pruritus, sweating

**Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dysphagia, dyspepsia, eructation, esophagitis, flatulence, gastrointestinal disorder, gastrointestinal hemorrhage, GGT increased, gum disorder, gum hemorrhage, vomiting

**Hematologic:** eosinophilia, lymphadenopathy

**Metabolic:** gout, weight loss

**Musculoskeletal:** arthralgia, arthritis, joint disorder, myalgia, myasthenia

**Respiratory:** dyspnea, increased cough, rales, pharyngitis, stridor

**Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, eye disorder, eye hemorrhage, tinnitus

**Urogenital/Reproductive:** dysuria, kidney calculus, nocturia, breast engorgement, polyuria, urogenital disorder, erectile dysfunction (ED).

The following adverse events have been reported rarely in patients given nifedipine in coat core or other formulations: allergic hepatitis, alopecia, anaphylactic reaction, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, hyperglycemia, jaundice, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, Stevens-Johnson syndrome, syncope, taste perversion, thrombocytopenia, toxic epidermal necrolysis, transient blindness at the peak of plasma level, tremor and urticaria.

#### OVERDOSAGE

Experience with nifedipine overdosage is limited. Symptoms associated with severe nifedipine overdosage include loss of consciousness, drop in blood pressure, heart rhythm disturbances, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary edema. Generally, overdosage with nifedipine leading to pronounced hypotension calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressor agents and fluids. After oral ingestion, thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. In cases involving overdosage of a slow-release product like nifedipine, elimination must be as complete as possible, including from the small intestine, to prevent the subsequent absorption of the active substance. Additional liquid or volume must be administered with caution because of the risk of fluid overload.

Clearance of nifedipine would be expected to be prolonged in patients with impaired liver function. Since nifedipine is highly protein bound, dialysis is not likely to be of any benefit; however, plasmapheresis may be beneficial.

There has been one reported case of massive overdosage with tablets of another extended release formulation of nifedipine. The main effects of ingestion of approximately 4800 mg of nifedipine in a young man attempting suicide as a result of cocaine-induced depression was initial dizziness, palpitations, flushing, and nervousness. Within several hours of ingestion, nausea, vomiting, and generalized edema developed. No significant hypotension was apparent at presentation, 18 hours post ingestion. Blood chemistry abnormalities consisted of a mild, transient elevation of serum creatinine, and modest elevations of LDH and CPK, but normal SGOT. Vital signs remained stable, no electrocardiographic abnormalities were noted and renal function returned to normal within 24 to 48 hours with routine supportive measures alone. No prolonged sequelae were observed.

The effect of a single 900 mg ingestion of nifedipine capsules in a depressed anginal patient on tricyclic antidepressants was loss of consciousness within 30 minutes of ingestion, and profound hypotension, which responded to calcium infusion, pressor agents, and fluid replacement. A variety of ECG abnormalities were seen in this patient with a history of bundle branch block, including sinus bradycardia and varying degrees of AV block. These dictated the prophylactic placement of a temporary ventricular pacemaker, but otherwise resolved spontaneously. Significant hyperglycemia was seen initially in this patient, but plasma glucose levels rapidly normalized without further treatment.

A young hypertensive patient with advanced renal failure ingested 280 mg of nifedipine capsules at one time, with resulting marked hypotension responding to calcium infusion and fluids. No AV conduction abnormalities, arrhythmias, or pronounced changes in heart rate were noted, nor was there any further deterioration in renal function.

Bradycardiac heart rhythm disturbances may be treated symptomatically with β-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

#### DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to each patient's needs. It is recommended that Nifedipine Extended-Release Tablets, USP be administered orally once daily on an empty stomach. Nifedipine extended-release tablets are an extended release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7 to 14 day period starting with 30 mg once daily. Upward titration should be based on therapeutic efficacy and safety. The usual maintenance dose is 30 mg to 60 mg once daily. Titration to doses above 90 mg daily is not recommended.

If discontinuation of nifedipine extended-release tablets is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Coadministration of nifedipine with grapefruit juice is to be avoided (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

Care should be taken when dispensing nifedipine extended-release tablets to assure that the extended release dosage form has been prescribed.

#### HOW SUPPLIED

Nifedipine Extended-Release Tablets, USP are supplied as 30 mg, 60 mg and 90 mg round, biconvex, film-coated tablets. The different strengths can be identified as follows:

Strength	Color	Markings
30 mg	Yellow	Debossed "677" on one side and Plain on the other side
60 mg	Yellow	Debossed "678" on one side and Plain on the other side
90 mg	Yellow	Debossed "679" on one side and Plain on the other side

Nifedipine extended-release tablets, USP are supplied in:

	Strength	NDC Code
Bottles of 100	30 mg	10370-677-01
	60 mg	10370-678-01
	90 mg	10370-679-01
Bottles of 500	30 mg	10370-677-05
	60 mg	10370-678-05
	90 mg	10370-679-05

The tablets should be protected from light and moisture and stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Dispense in tight, light-resistant containers.

Manufactured by:  
**Par Pharmaceutical**  
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